Process Validation: A Product Reviewer's Perspective

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Background

- Focus on a limited areas of process validation and the issues that have arisen
- Case studies from 483s and submissions where problems developed
- PAT may influence the level of process validation
- Talk is not intended for implementation of new regulatory requirments

Presentation Outline

- General Background on Process Validation
- Case Studies by Type of Study
  - Background
  - Case Studies
  - Conclusions
- Implications for role of QA

Process Validation

- Definition: Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes

Comprehensive Quality Control Strategy

Process → Product Testing

- Facilities and Equipment
- Control of Raw Materials
- In-Process Controls
- Process Validation
- cGMPs (QC/QA)

- Method Validation
- Characterization
- Release Testing
- Stability Testing

Quality Assurance

- Quality Assurance responsibilities include approving or rejecting all procedures impacting on the identity, strength, quality and purity of the drug product.
- These responsibilities would include process validation studies
  - Sign off of validation protocols
  - Sign off of validation reports
  - Sign off of investigations of deviations from the validated process
  - Role in developmental studies undefined

Process Validation Studies (product reviewer oversight)

- Process Consistency
- Viral Clearance
- Impurity Removal
- Hold Times
- Mixing Studies
- Operating ranges for unit operations
- Performance measures
- Resin reuse

Process Validation

Types of samples

- Production lots
  - Conformance lots evaluated in detail to demonstrate consistency
- Small scale studies
  - Limit of in vitro cell age (not always)
  - Hold times for process intermediates

Process Validation

- Lab scale studies
  - Spiking studies (Viral and impurity removal)
  - Process characterization of operating ranges
    - Identification of critical operating parameters
    - Establishment of limits for operating parameters
    - Performance indicators (parameter and limits)

Case Studies

- Looked at a variety of 483 observations from pre-license, pre-approval and biennial inspections (DTP/DMA) and “institutional” review memory
- There is a disparity between biennial and pre-license inspections (older versus recent products)
- Concentrated on issues that are common to biotech products in general

Conformance Lots

- Critical element in formal validation of process consistency
- Prerequisites to producing conformance lots
- Typical minimal is 3 consecutive production lots following approved batch records but evaluated in detail
- For changes to an approved application the evaluation in detail may be limited to the operations that are impacted by the change
- Additional batches may be required (multiple bioreactors)
- Typical to target the set point and not the extremes of the operating ranges

Conformance Lots (failures)

"Process validation for the XXX was not complete in that three successful consecutive lots were not manufactured" (483 observation)

Causes:

- Contaminations and rejections of material
- Lots fail specification

- Request for additional Conformance lots case by case, if cause is assignable and does not impact conclusions about process validation you may be able to separate failed validation from the successful portions

Conformance Lots (study failures)

Case Study - Validation of Roller Bottle inoculum

- Validation protocol with Pre-defined procedures and acceptance criteria
- Additional monitoring of many Roller Bottles for cell #
- During monitoring trends were observed and inoculum was manually altered based on in-process data
- All AC were achieved but manual manipulation was not part of the protocol
- Problem corrected and next run was fine
- Protocol was not followed for number of replicates
- Agency requested additional study but not an additional conformance lot

Conformance Lots (successful)

- For BLA application manufacturer provided data on three qualification lots and a few additional batches of drug substance.
- All lots met predefined acceptance criteria
- Subsequent manufacture high rate of failures (5/9 lots) due to bacterial contaminations across different bioreactors
- Process could be viewed as “controlled” because there was sufficient oversight to prevent any impact on the quality of product released
- Is there a high degree of assurance that the process will consistently produce a product that meets its expected quality characteristics?
- Process required revalidation resulting in delay of approval

Conformance Lots (successful)

- For a change in media composition manufacturer provided data from 3 qualification lots
- Lots met the acceptance criteria but trended high in one quality attribute but was within the historical experience
- Several subsequent lots failed one release test

Take Home Message

- Conformance batches provide evidence to support the validity and consistency of the process but;
- A process is not truly “validated” when you have not introduced all causes of variation into the process

- Process validation is an activity that should continue throughout the entire life cycle of the product

Missing Validations

- Stability of process intermediates
- Worst case hold times?
- Process solution stability
- Mixing studies
- Resin reuse/membrane lifetime studies
- Operating parameters (Identification and establishing appropriate limits)
- Performance parameters

Process Control Parameters

- Operating parameters: conditions that can be directly controlled or manipulated during manufacture (e.g. pH, temperature, protein load, column flow rate and conductivity)
- Performance parameters: measurements of a unit operation's performance (e.g., product quality attributes step yield, cell viability, cell number and pH)

For process validation:

- Establishing operating ranges for the critical parameters in a process and demonstrating that operating within those limits will produce a product that meets specifications

Defining Operating Parameters

- The function of the operation unit should be identified
- Critical operating parameters should be identified and appropriate limits set
- Operating parameters should be challenged at the expected process variability (process capability) in development studies
- Evaluation of the interrelationship between parameters is critical to appropriate validation

Operating Parameters

"in sufficient in-process controls to assess XXX performance" (483 observation)

- Failure to evaluate (or identify) the acceptable range of pH, (flow rate, ionic strength, protein load) for YYY chromatography step

Root cause: lack of process characterization/understanding

Process should be characterize in development

Incomplete validations are exposed frequently when non-conformance events occur

Column Operating Parameters (Case Study)

- When protein loads approached the columns established upper limit, protein bound as expected but on elution because of the high concentration of protein released, the product precipitated
- Range for protein load was set based on binding capacity of the resin and resin amount
- What goes on will come off – incomplete assessment of the unit operation

Operating/Performance Parameters (CS)

- Chromatographic profile of the 1st chromatographic column changed both qualitatively and quantitatively
- Followed an increased scale of fermentation and the inability of the UF/DF unit to achieve pH values in accordance with previous history
- Operating range for pH of column load was wide and had not been evaluated in process characterization studies
- Manufacturer did not fully understand the operation of the UF/DF unit and had not established appropriate performance indicators due to lack of validation of the downstream process

Operating Parameter (CS)

- In evaluating a process change that potentially could affect product aggregation, one conformance lot failed for aggregate content
- Failure was associated with a out of trend in the pH step for viral inactivation
- Retrospective analysis showed that all lots similarly out of trend for pH had also failed aggregation spec
- Step appeared to have been “appropriately” characterized for the acceptable pH range
- This and additional info convinced the agency that the failure was not associated with the process change and approved the change with revised limits for pH.

Operating Parameter

- Overall calculation of viral inactivation was not affected
- There is the expectation that developmental studies would be performed to confirm the retrospective analysis
- Quality system oversight should have identified the trend earlier
- Cause for the disparity is not clear
  - In appropriate mixing
  - Failure to identify all factors involved (e.g. protein concentration, ionic strength and temperature)
  - A multi variant or worst case analysis should have been performed

Clearance Studies

- Impurities removal are validated through in-process testing of intermediates in conformance lots and
- Laboratory scale spiking studies (excess capacity)
- If level of impurities are “well control” then spiking studies may not be necessary

  Example: DNA levels entering system may be variable but may also be able to establish the limits of that variability

Clearance Studies (CS)

- One intended function of the chromatography step was to eliminate endotoxin
- Manufacturer monitored endotoxin entering and leaving unit operation on 3 consecutive production lots
- Results: little endotoxin entered the system but for 2 lots output of endotoxin was greater then the input
- Data is uninterpretable

Spiking Studies*

- Scale down processes must be representative and operated equivalent to that of the production scale

"Validation study did not include an evaluation that that the scale down version of XXX was representative of the manufacturing process" (483 Observation)

- As appropriate data was not collected during study, data derived from the spiking study was useless

Validation of Adventitious Agents

- Manufacturer monitored adventitious agents during process of 3 consecutive lots
- Results showed no adventitious agents
- They no longer would routinely test for these agents
- Appropriate control of AA, requires routine monitoring at steps likely to introduce or propagate these agents

QA level of Oversight

- Check box – a study was done
- Some review of study content – Does the study make sense?
- Review of content requires expert knowledge

  - knowledge need not reside in QA but they should have access to expertise independent of those conducting the study